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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,721	10/26/2001	Naohiro Terada	5853-207	9675

7590 09/10/2003

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EXAMINER

KELLY, ROBERT M

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/045,721	TERADA ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- **Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 24 June 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \*   c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                              | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                     | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. | 6) <input type="checkbox"/> Other: _____.                                   |

***Information Disclosure Statement***

The information disclosure statements (IDS) submitted on 01 April 2002 and 24 June 2002, were both filed before the mailing date of the first action on the merits on 8 September 2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

***Claim Objections***

Claim 5 is objected to because of the following informalities: the claim appears to be missing a verb, i.e., "are"; also, the claim uses the plural "stems" where it appears the proper term is singular, i.e., "stem". Appropriate corrections are required.

Claim 20 is objected to because of the following informalities: the claim uses the gerund "performing" where it appears to require the use of the passive verb "performed". Appropriate correction is required.

Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim states that the conditions that would promote tissue-specific differentiation ... comprises culturing ... in a differentiating medium. The specification defines "differentiating medium" as any medium that at least does not prevent differentiation of stem cells (SPECIFICATION, p. 3, lines 19-20). Furthermore, conditions that would promote differentiation of stem-cells if an agent that promoted tissue-specific differentiation was in contact with the stem cells (from depending claim 1) would be such a differentiating medium. If

the medium prevented differentiation, such an agent would not promote differentiation, and the invention would be inoperative.

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7-9, and 13-19 are rejected under 35 U.S.C. 102(b) as being anticipated by WIPO Document No. 99/10535 to Liu, et al., hereinafter referred to as Liu '535.

Claims 1, 7-9, and 13-19 disclose methods to screen substances for the ability to promote cellular differentiation in stem cells in which cultured stem cells are contacted with a test substance, cultured, and tested for cellular markers of differentiation. The claims further require at least two separate cultures, each contacted with a different substance, and testing for increased tissue-specific gene expression as the cellular marker of differentiation. Dependent claims limit the culturing to 37° C, humidified and carbon-dioxide-containing environments, to performing the experiments in 96-well plates, and the method of measuring cellular changes in mRNA expression, wherein such measuring can include isolation of total cellular RNA, cellular mRNA, reverse transcription to obtain cDNA, PCR amplification, immobilization of mRNA, and probing for specific mRNAs.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 inherently discloses all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535, ABSTRACT). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression

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profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreover, Liu '535 inherently teaches the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place.

Liu '535 also inherently teaches the use of 37° C as a culturing temperature, as well as humidified, carbon-dioxide containing environments, as these are standard culture conditions.

Liu '535 also teaches the aspects of mRNA isolation (p. 20), total cellular RNA isolation (p. 20), reverse transcription (p. 20), PCR amplification (pp. 23-24), immobilized mRNA (EXAMPLE 4), and probing for mRNA (EXAMPLE 4).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2-5 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of U.S. Patent No. 5,874,301 to Keller, et al., hereinafter referred to as "Keller '301".

Claims 2-5 encompass the screening technique of Claim 1, and further limit the screen to (i) embryonic stem cells, (ii) mammalian embryonic stem cells, (iii) murine embryonic stem cells, and (iv) murine R1 cells. Claims 10-12 further limit the time of culturing the cells to more than 5, 7, or 1-18 days.

Liu '535 does not teach these cell-type limitations, as it is directed to stem cells in general; however, Keller '301 teaches the isolation of embryonic cell populations (TITLE) and specifically teaches embryonic stem cells (col. 2, lines 5-8). Keller '301 also teaches mouse embryonic stem cells (Example 1). Mice are mammals, therefore, the limitation of mammalian embryonic stem cells is also taught. Keller '301 also teaches mouse embryonic stem cells in general (col. 2, lines 5-36), therefore one would have been motivated to use any mouse embryonic stem cell in practicing the invention, including mouse R1 embryonic stem cells. Lastly, Keller '301 teaches that preferred culture times are between 5 and 12 days (col. 9, lines 54-64).

Keller '301, is also a reference that one of ordinary skill in the art at the time of the invention would have utilized to modify the teachings of Liu '535, and therefore obviates the above-listed claims. This is because Keller '301 specifically teaches that "[t]he cells are useful ... to identify compounds that control precursor cell growth and differentiation." Therefore, one of ordinary skill in the art would have modified Liu '535 to provide a method of screening compounds for cell growth and differentiation utilizing the embryonic stem cells as limited in the

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claims. Moreover, the artisan would have had a reasonable expectation of success, as Liu '535 teaches how to define the system (ABSTRACT), and Keller '301 shows that these cells have been shown to undergo differentiation (col. 2, lines 5-33).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of Thomson, et al. (1998) Science, 282:1145-1147, hereinafter referred to as "Thomson '98".

Claim 6 encompasses all the limitations of Claim 1, and further limits the cell type to human embryonic stem cells.

Liu '535 does not teach human embryonic stem cells; however, Thomson '98 teaches primate embryonic stem cells (TITLE), which includes the specific teaching of human embryonic stem cells (ABSTRACT).

Furthermore, one of ordinary skill in the art at the time of invention would have been motivated to modify the teachings of Liu '535 by the use of human embryonic stem cells as taught in Thomson '98, because Thomson '98 teaches that such embryonic stem cells are useful for drug discovery (ABSTRACT). Similar to the arguments for the combination of Keller '301 with Liu '535, the artisan at the time of the invention would have also had a reasonable expectation of success because Thomson '98 demonstrates that these cells are capable of differentiation (p. 1146).

Therefore, Claim 6 is unpatentable.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of U.S. Patent No. 5,143,854 to Pirrung, et al., hereinafter referred to as "Pirrung '854".

Liu '535 teaches all of the limitations of depending Claim 1, as discussed above, however Liu '535 does not teach the aspect of utilizing gene chip technology in the screening for tissue-specific gene expression; however, Pirrung '854 teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung '854 teaches that such technology is useful for "[s]creening large numbers of polymers for biological activity," (col. 3, lines 39-41).

Moreover, one of ordinary skill in the art at the time of the invention would have been motivated to modify the teachings of Liu '535 by the gene chip technology of Pirrung '854 with a reasonable expectation of success because the gene chip technology of Pirrung '854 allows for the controlled synthesis of a variety of polymers in a small space (SUMMARY OF INVENTION), which is particularly suited to the screening system described. Also, because both Liu '535 and Pirrung '854 have been shown successful, one would have expected success with their combination.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (703) 305-4460. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.



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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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